

### REMARKS

As requested, the status of the applications from which priority is claimed has been added to the specification. No amendment to the claims has been made except to delete an obviously misplaced comma in claim 1.

The handwritten alteration "-See ex 10" on page 63, line 10, was not made by the applicant. It is extraneous and should be deleted.

#### *S. coelicolor* Strain CH999

Applicants agree that CH999 is required for the practice of claims 7 and 18. This strain is readily available to the public. This is evident, for example, from one of the documents cited by the Office: Kao, C. M., *et al.*, *Science* (1994) 265:509-512. This strain is mentioned on page 510, first full paragraph of the right-hand column referring an earlier paper that describes this strain: McDaniel, R., *et al.*, *Science* (1993) 262:1546. As materials published in *Science* must be accessible to the public, this demonstrates that the strain is available.

#### The Rejections Under 35 U.S.C. § 103

Claims 1-11 were rejected as assertedly obvious over the combination of Kao, *et al.*, cited above, in view of Donadio, *et al.*, *PNAS USA* (1993) 90:7119-7123 and Donadio, *et al.*, *Gene* (1992) 115:97-103.

The Office is entirely correct that the invention of applicants permits the use of a diketide starter (rather than an acyl starter) without contamination by synthesis carried out by virtue of the ability to incorporate the naturally occurring starting material. Respectfully, applicants are unable to find any suggestion in the combination of Kao and the two Donadio publications to modify a

PKS to achieve this result. While it could be argued that there might be a reasonable expectation of success *once applicants thought of doing this*, it appears there is no suggestion in the art itself to make the claimed modification.

The primary document, Kao, as the Office correctly states, indicates that there is some flexibility on the part of the erythromycin PKS with respect to its ability to incorporate alternative acyl starter units. What this has to do with incorporation of diketides is entirely unclear. If anything, Kao suggests that an altered PKS could be obtained simply by substituting a non-native starting unit for that which occurs naturally, which is not at all what applicants have done.

Both Donadio documents say substantially the same thing: It appears that altering the reductive cycle in a module so that a modified product is formed by that module does not destroy the ability of subsequent modules to accommodate the modified form. It is unclear how this leads to any suggestion of inactivating the ability of the PKS to utilize its native starter unit. It is also unclear how these documents make any suggestion that the synthesis be started by supplying a diketide rather than the acyl starter unit.

It may be correct, as the Office asserts, that the combined teachings of these documents would lead one to believe that modified forms of PKS could be synthesized by altering the PKS enzymes and that the enzymes in the synthesis sequence are not overly particular about the exact structure of the substrate on which they operate. This falls far short of a suggestion to feed diketides and obstruct competing synthesis which would progress from the native starting material.

Where, in *any* document, is there a suggestion that the ability of the PKS to incorporate its native starting unit be destroyed? Where is there a suggestion in any cited document that a diketide

be used in the synthesis? Neither suggestion is there in any document taken alone or in all the documents taken together.

No response would be complete without also pointing out that there appears to be no motivation to combine Kao with the two Donadio documents. For what purpose would they be combined? Applicants find no rationale cited by the Office for making the combination other than “due to the added flexibility with regard to engineering the final product of this PKS system.” Applicants are unsure what this means. In any case, it is quite clear that if indeed Kao were combined with the two Donadio documents, all that would be taught is that alternate acyl starting materials might be used and that it might be possible to modify individual modules so that the condensations and optional reduction cycles would be different from that in the native PKS. That is not the invention here, as is evident from a straightforward reading of claim 1.

While applicants do not rely on particular limitations in dependent claims for patentability, they are puzzled by the comment that the nature of the diketide substrates named in claims 8-11 would have been obvious “in the course of optimization.” Applicants are unable to find any mention of any diketide substrate of any kind in any document cited by the Office.

In view of the foregoing, applicants believe the rejection of claims 1-11 may properly be withdrawn.

#### Double-Patenting

Claims 12-22 were rejected as asserted obviousness-type double-patenting over claims 1-9 of U.S. 6,274,560. A terminal disclaimer is provided with respect to this patent.

Claims 12-22 were also rejected as assertedly obviousness-type double-patenting over U.S. 6,531,299 ('299), claims 1-15. Respectfully, applicants fail to see how this rejection can be

correct. There is nothing in the claims of the '299 patent that speaks to the invention presently claimed. The claims in '299 are directed to cell-free synthesis using polyketide synthases in general; there is nothing at all in these claims about utilizing diketide substrates or destroying the ability of a PKS to utilize its native starter unit. Applicants respectfully request this basis for rejection be withdrawn.

### Conclusion

Applicants believe they have shown that there is no suggestion in the combination of Kao with the two Donadio documents, even if motivation exists to combine them, to destroy the ability of a PKS to utilize its native starter unit and to supply a diketide as the primary unit on which condensation will occur. A terminal disclaimer has been submitted with respect to U.S. 6,274,560, but it is believed the double-patenting rejection over 6,531,299 is in error. Applicants respectfully request that claims 1-22 be passed to issue.

If minor matters remain which could be resolved over the telephone, a call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 300622000205.

Respectfully submitted,

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By: Kate H. Murashige  
Kate H. Murashige  
Registration No. 29,959  
MORRISON & FOERSTER LLP  
12531 High Bluff Drive  
Suite 100  
San Diego, California 92130-2040  
Telephone: (858) 720-5112  
Facsimile: (858) 720-5125